Randomized Controlled Trial on Nondescent Vaginal Hysterectomy and Total Laparoscopic Hysterectomy versus Total Abdominal Hysterectomy: A Cost-effectiveness Analysis

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ABSTRACT

Aim and objective: Hysterectomy is the commonest major gynecological procedure. There is little information from randomized controlled trials (RCTs) in low-resource settings. Therefore, the aim was to study outcomes and cost-effectiveness of nondescent vaginal hysterectomy (NDVH) and total laparoscopic hysterectomy (TLH) versus total abdominal hysterectomy (TAH).

Materials and methods: A pragmatic multicenter three-arm (49 per arm) RCT was done on patients needing hysterectomy for benign uterine causes. Exclusion criteria were uterus larger than 14 weeks, previous pelvic surgery, any medical illness that contraindicated laparoscopy, and any patient requiring surgery for incontinence or uterovaginal prolapse. The main clinical outcome measure was time to recover. Incremental cost-effectiveness ratios (ICERs) were calculated for NDVH and TLH. Cost-effectiveness acceptability curves of NDVH and TLH were formulated.

Results: There was no significant difference in time to recover [median (inter-quartile range) days] [TAH, 35 (30–45) days; NDVH, 32 (24–60) days; and TLH, 30 (26–45) days, $p = 0.89$]. The direct cost (USD) of TAH [659 (632–687)] was significantly lower compared to NDVH [800 (622–1116)] and TLH [752 (719–795)] ($p = 0.03$). The ICER$_{NDVH}$ showed TAH was dominant. ICER$_{TLH}$ was 11 USD/day. Worst-case scenario ICERs showed that TAH was dominant. NDVH and TLH were dominant to TAH in the best-case scenario.

The probability of cost-effectiveness (threshold of 3 USD/day) was 1.15 versus 0% in the study setting, 0.2 versus 0% in the worst-case scenario, and 76.1 versus 79% in the best-case scenario for NDVH and TLH, respectively.

Conclusion: The main clinical outcome, time to recover, showed an insignificant difference between TAH, NDVH, and TLH. However, when considering cost-effectiveness, TAH is likely to be the cost-effective method for the generalist, while the alternate routes NDVH and TLH are likely to be cost-effective in specialized centers.

Keywords: Cost-effectiveness analysis, Nondescent vaginal hysterectomy, Randomized controlled trial, Total abdominal hysterectomy, Total laparoscopic hysterectomy.

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INTRODUCTION

Hysterectomy is the commonest major gynecological procedure.[1,2] The rate of hysterectomy in resource-poor settings like Sri Lanka is likely to be high due to the non-availability of novel minimally invasive treatment methods, such as endometrial ablation and levonorgestrel intrauterine system.

The route of hysterectomy depends on the pathology, size and descent of the uterus, presence of endometriosis, the likelihood of adhesions, previous pelvic surgery, surgeon's preference, and patient's choice.[3,4] However, there is a ubiquitous group of patients for whom total abdominal hysterectomy (TAH), nondescent vaginal hysterectomy (NDVH), or total laparoscopic hysterectomy (TLH) can be done.

However, when considering hysterectomy routes, most comparisons are between abdominal and laparoscopic hysterectomy with little information on vaginal hysterectomy.[5-8] There is also a dearth of evidence on randomized controlled trials (RCTs) and cost-effectiveness analyses in low-resource settings.[9]

The objective of this study was to find out the optimal route of hysterectomy in this group of patients in terms of clinical outcomes and cost-effectiveness through an RCT between the three main routes: NDVH, TLH, and TAH.

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MATERIALS AND METHODS

A pragmatic multicenter three-arm (TAH, NDVH, and TLH) RCT was done following the principles of good clinical practice.

Flowchart 1: Participant flow diagram
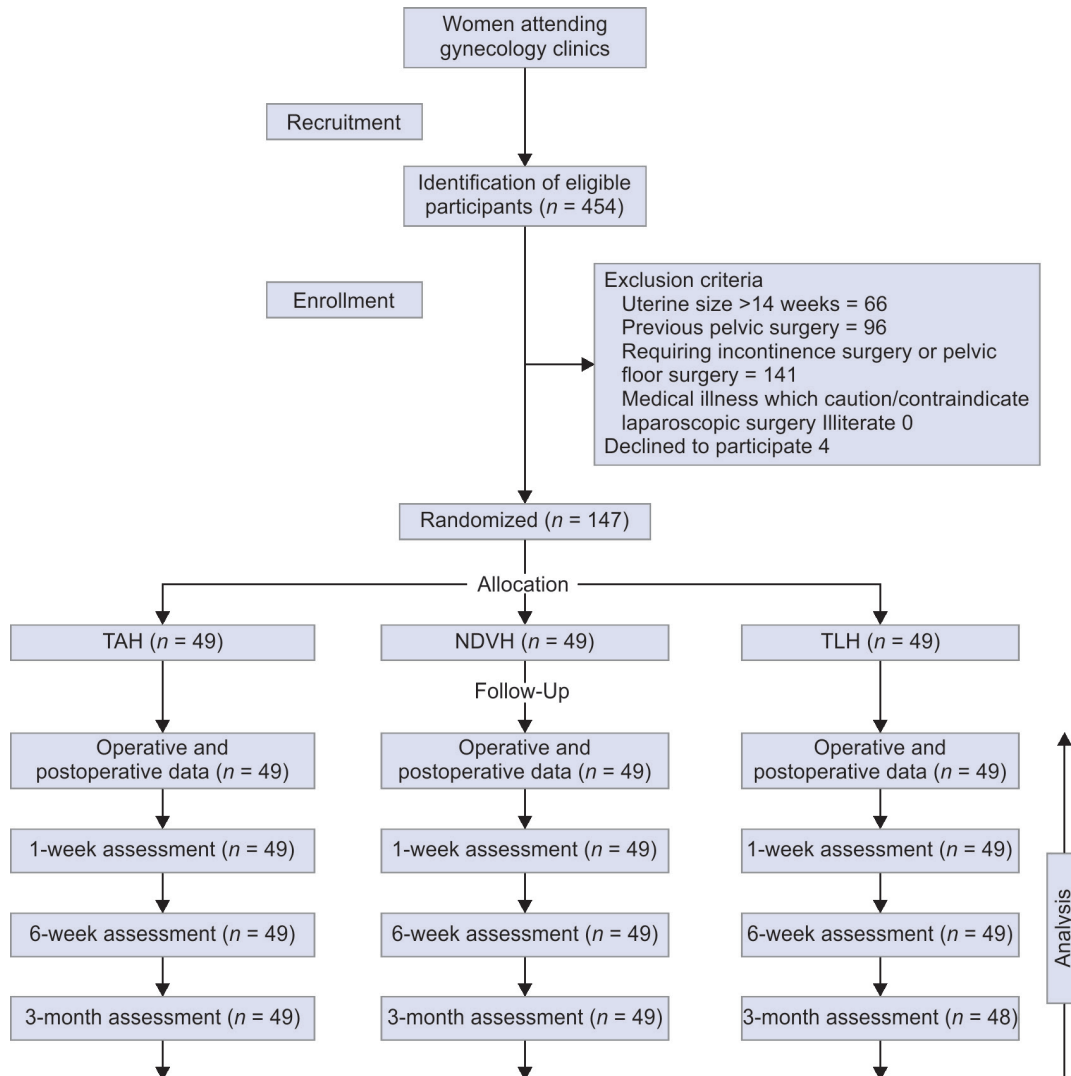
Consolidated standards of reporting trials (CONSORT) is attached as supporting information 1.[10] An economic evaluation was also done as per accepted guidelines (CHEERS checklist—supporting information 2).[11] The study settings were the professorial gynecology unit of the North Colombo Teaching Hospital, Ragama, and the gynecology unit of the District General Hospital, Mannar, Sri Lanka. The data presented in this study were collected from August 1, 2016, to October 31, 2018. The study protocol was published.[3]

Eligible participants required hysterectomy for benign uterine causes. Exclusion criteria were uterus larger than 14 weeks, previous pelvic surgery, any illness that contraindicated laparoscopy, and any patient requiring surgery for incontinence or uterovaginal prolapse. Eligible patients were randomly assigned to undergo NDVH, TLH, or TAH. The exposure variables were TLH and NDVH with the control group undergoing TAH (Flowchart 1). Patients who declined participation in the study had TAH (standard treatment).

A type I error of 0.01 with a power of 80% and a possible loss to follow-up rate of 20% in order to detect a difference of 7 days in time to recover between TAH, NDVH, and TLH necessitated a sample size of 147 patients (49 per arm).[12] In order to keep the overall p-value less than 0.05 after pairwise comparisons, a Bonferroni adjustment for multiplicity with a type 1 error of 0.01 (two-sided) was required.

At each site, block randomization in multiples of three was done by opening sealed opaque envelopes containing computer-generated block randomization numbers to ensure approximately equal numbers in each arm at any given point of the study.

The primary outcome measure was time to recover following hysterectomy, which was considered as the earliest time to resume activities done prior to surgery (e.g., cooking, washing clothes, occupation, and sexual activity). Other outcome measures were operative time, blood loss, pain scores, complications, postoperative hospital stay, direct cost, and cost-effectiveness.

Data were obtained from clinical records. Patients were followed up either until time to recover or up to 6 months, whichever was longer. Data analysis included all patients and was based on the intention-to-treat principle. Data were checked for normality, and nonparametric tests were adopted as it did not follow a normal

distribution. The primary outcome, time to recover, was assessed using a Kaplan–Meier survival analysis. The end point was time to recover. Differences in survival distributions were analyzed using a log-rank test.

The other outcomes such as operative time, blood loss, pain scores, postoperative hospital stay, and cost were analyzed using Kruskal–Wallis test with post hoc comparisons. Complications were graded based on their severity as follows: no complication (1), minor infection or blood transfusion (2), laparotomy (3), visceral injury, or fistulae (4). If a patient had more than one complication, the sum of all the complications was considered.

Missing cost data were not excluded for the economic evaluation. Multiple imputations were used to overcome missing data. The distributions were checked for normality, and bootstrapping with 1,000 repetitions from the study distributions was taken to reveal the joint distribution of cost and effect for all three arms of the trial. The costs are reported in USD. Non-tradeable goods (labor and utilities) were recalculated using purchasing power parity factor of 48.28 for 2017.[13] The exchange rate (1 USD = LKR 144.9625) was used for equipment, drugs, and investigations, which were tradeable commodities.

A micro-costing approach was adopted to calculate direct hospital costs from the time of presentation to the gynecology clinic. The preoperative costs, operative costs, cost of hospital stay, and costs up to 6 months after surgery were considered for direct hospital costs. Labor costs were calculated using a time-driven, activity-based method. Equipment, investigations, and utility costs were calculated using a top-down method. Bottom-up micro-costing was used for drug costs. The method used for cost estimation in this study was published.[14]

In order to assess the robustness of costing assumptions, a deterministic sensitivity analysis was used. The worst-case scenario considered a 5-year shelf life instead of 10 years for equipment, an extra 30 minutes of operating time, one extra postoperative day, doubling of the cost of complications, doubling of the cost of readmissions, and doubling of utility costs with a discounting rate of 10%.[15] The best-case scenario considered a 10-year shelf life for equipment, 30 minutes shorter operating time, and one day shorter postoperative hospital stay, with no complications or readmissions, at a discounting rate of 10%.

The incremental cost-effectiveness ratio (ICER) for the study data was estimated using mean cost for the intervention arm (either TLH or NDVH) minus the mean cost for the standard treatment arm (TAH) divided by the meantime to recover of the intervention arm (either TLH or NDVH) minus the meantime to recover of the standard treatment arm (TAH).

The ICERs for the worst-case scenario were estimated against the first quartile (Q1) values of time to recover and costs of TAH. The ICERs for the best-case scenario were estimated against the third quartile (Q3) values of time to recover and costs of TAH.

Cost-effectiveness acceptability curves of NDVH and TLH were drawn for the three scenarios (study setting, best-, and worst-case scenarios) using the probability of cost-effectiveness on the y-axis and ceiling ratios of cost (USD/day) on the x-axis.

Results

The study outline is shown in Flowchart 1. Out of the 147 patients, 71 were from Mannar (TAH, 24; NDVH, 23; and TLH, 24), while 76 were from Ragama (TAH, 25; NDVH, 26; and TLH, 25). Over 6 months of follow-up, 145 patients out of 147 completed all the assessments. In the TLH arm, one patient from Mannar was lost to follow-up after 6 weeks. In the NDVH arm, one patient from Mannar was lost to follow-up after 3 months. The three groups, TAH, NDVH, and TLH, had similar basic characteristics (Table 1).

There was no difference in time to recover [median (interquartile range)] among TAH [35 (30–45) days], NDVH [32 (24.5–60) days], and TLH [30 (25.5–45) days], respectively (log-rank test $X^2(2) = 0.242$, $p = 0.89$, Table 2). The time to recover is shown in a Kaplan–Meier plot (supporting information 3). Post hoc comparisons between TAH, NDVH, and TLH were done using COX regression. Analysis of covariates showed that the severity of complications was significantly associated with time to recover (for one increase in complications score, a 25% increase in time to recover, HR = 0.75, $p = 0.04$). However, age (HR = 1.00, $p = 0.86$), BMI (HR = 1.02, $p = 0.29$), parity (HR = 1.01, $p = 0.87$), operative time (HR = 1.00, $p = 0.52$), change in hematocrit (HR = 0.99, $p = 0.68$), day one pain scores (HR = 0.97, $p = 0.74$), day two pain scores (HR = 0.98, $p = 0.76$), or postoperative hospital stay (HR = 0.98, $p = 0.85$) was not associated with time to recover. A faster time to recover was observed for NDVH and TLH at Mannar compared to Ragama [NDVH HR = 4.66, $p < 0.01$, and TLH HR = 4.66, $p < 0.01$] (supporting information 4).

The operative time and time under anesthesia were significantly longer in patients undergoing TLH compared to those undergoing TAH or NDVH (Table 2, Kruskal–Wallis test, $p < 0.001$). However, patients undergoing TLH had a shorter postoperative hospital stay [2 (1–3) days] compared to those undergoing NDVH [3 (2–3) days] and TAH [3 (2–3) days] (Table 2, Kruskal–Wallis test, $p < 0.001$). The risk of hemorrhage was similar in the three groups. The TLH group had significantly lower pain scores on days one and two compared to NDVH and TAH groups (Table 2, Kruskal–Wallis test, $p < 0.01$).

When considering major complications, three patients in the NDVH group needed subsequent laparotomies (two for bladder injuries and one for internal bleeding), and one patient had a serosal rectal injury. When considering major complications in the TLH group, there was one ureteric injury and two laparotomies (Table 2). The patient with the ureteric injury in the TLH group developed an ureterovaginal fistula. One patient with a bladder injury in the NDVH group developed a vesicovaginal fistula. There were no major complications in the TAH group. These complicated cases are outliers in the survival analysis for the TLH and NDVH arms (supporting information 3).

Table 1: Basic characteristics

	TAH (n = 49)	NDVH (n = 49)	TLH (n = 49)	p value
Age (years) [mean, (95% CI)]	47.0 (45.6–48.4)	47.1 (44.8–49.5)	48.1 (46.2–50.1)	0.63[#]
BMI (kg/m²) [mean, (95% CI)]	26.4 (24.8–28.0)	25.7 (24.2–27.1)	25.0 (23.3–26.7)	0.51[#]
Median parity (Q1–Q3)	2 (2–3)	3 (2–3.5)	3 (2–3.5)	0.20*
Uterine weight (g) [median (Q1–Q3)]	124 (90–252)	111 (91–153)	141 (101–199)	0.16*

[#]One-way analysis of variance; *Kruskal–Wallis test

Table 2: Clinical outcomes[#]

	TAH (n = 49)	NDVH (n = 49)	TLH (n = 49)	p value*
Anesthetic time (min)	85 (65–100)	75 (64–100)	135 (116–152)	<0.001
Operative time (min)	45 (36.5–60)	50 (35–65)	93 (80–111)	<0.001
Postoperative hospital stay (days)	3 (2–3)	3 (2–3)	2 (1–3)	<0.001
Blood loss (mL)	150 (100–200)	150 (100–275)	150 (100–300)	0.51
Change in hematocrit	1.8 (0.8–3.8)	2.7 (1.2–5.1)	1.9 (1–3.2)	0.30
Pain score—day 1	7 (5.5–8.2)	6 (5–7)	5 (4–6.8)	<0.01
Pain score—day 2	4 (3–5.5)	3 (2–4.7)	3 (1–4)	<0.01
Pain score—day 3	1.2 (0–4)	1 (0–2)	0 (0–2)	0.14
Time to recover (median, Q1–Q3) (days)	35 (30–45)	32 (24.5–60)	30 (25.5–45)	0.89[¨]
Time to recover (mean, 95% CI) (days)	40.43 (34.91–45.95)	41.73 (33.31–50.16)	41.06 (31.06–51.07)	0.98[±]
QALYs (AUC)	8.63 (2–15.27)	9.97 (1.9–18.03)	13.84 (7.08–20.61)	
Complications				
No complications	42	41	37	
Laparotomy	0	3	2	
Blood transfusion	5	6	5	
Bladder injury	0	2	0	
Ureteric injury	0	0	1	
Rectal injury	0	1	0	
Postoperative fever	2	0	2	
Surgical site infection	1[i]	1[i]	0	
Urinary tract infection	0	0	2	
Histology				
Leiomyoma	20	12	13	
Adenomyosis	06	10	09	
Leiomyoma and adenomyosis	06	06	05	
Proliferative/secretory endometrium	07	11	17	
Other	10	10	05	

[#]Median (Q1–Q3); *Kruskal–Wallis test; [¨]Log-rank test; [±]ANOVA; [↓]Patients can have one or more complication; [i]Superficial incisional surgical site incision (SSI), the SSI incidence was 2.04% for TAH and NDVH. The SSI was 0% for TLH. Standardized infection rate was 1.67 for TAH and NDVH[18]

The direct cost (USD) of TAH [659 (632–687)] was significantly lower compared to NDVH [800 (622–1116)] and TLH [752 (719–795)] ($p = 0.03$). Study data for $ICER_{NDVH}$ [mean, 95% confidence interval (CI)] showed that TAH was dominant (TAH dominant to 477 USD/day). $ICER_{TLH}$ was 11 USD/day (TAH dominant to 351 USD/day) (Table 3). The probability of cost-effectiveness at a threshold of 3 USD/day was 1.15 and 0% for NDVH and TLH, respectively. The corresponding values at a threshold of 10 USD/day were 14.1 and 4.2% for NDVH and TLH, respectively (Fig. 1).

Worst-case scenario ICERs (mean, 95% CI) showed that TAH was dominant (TAH dominant to TAH dominant) for $ICER_{NDVH}$ and $ICER_{TLH}$ (Table 3). The probability of cost-effectiveness was unchanged at 0.2 and 0% for NDVH and TLH at a threshold of 3 and 10 USD/day, respectively (Fig. 1).

The best-case scenario for $ICER_{NDVH}$ (mean, 95% CI) showed that NDVH was dominant (TAH dominant to 874 USD/day). $ICER_{TLH}$ showed that TLH was dominant (TAH dominant to 686 USD/day) (Table 3). The probability of cost-effectiveness at a threshold of 3 USD/day was 76.1 and 79% for NDVH and TLH, respectively. The probability of cost-effectiveness at a threshold of 10 USD/day was 76.3 and 79% for NDVH and TLH, respectively (Fig. 1).

DISCUSSION

There was an insignificant difference in time to recover between TLH, NDVH, and TAH. This was because the study was only powered to detect a difference of 7 days or more. The study findings also showed that TAH was the preferred route as the direct cost was lower with no difference in effect compared to alternate routes. TAH was preferable in the worst-case scenario as both cost and effect were superior to NDVH and TLH. NDVH and TLH both were preferable to TAH in the best-case scenario.

This in contrast to the Cochrane review that suggests that vaginal hysterectomy has a faster recovery compared to abdominal hysterectomy.[16] However, there were considerable differences in the operative time, pain scores on the first 2 days, and postoperative hospital stay between the three groups.

A differential expertise bias favoring TAH would need to be considered because even though being competent in all three routes, the competency for TAH would have been higher than for either NDVH or TLH. This issue arises because of the unique nature of surgical training in resource-poor settings such as Sri Lanka where competency for open surgery is acquired prior to minimally invasive surgery. An expertise-based RCT in a specialized center may find alternate routes, NDVH and TLH, to be more cost-effective as it is likely to represent the best-case scenario.

When measuring the effect, quality-adjusted life years were not considered as the main outcome measure as it required an impractical sample size. Furthermore, it is also not a realistic indicator as it assigns a patient to a specific health state that may be inaccurate and not match societal preferences.[15,17] The World Health Organization developed disability-adjusted life years. However, it is
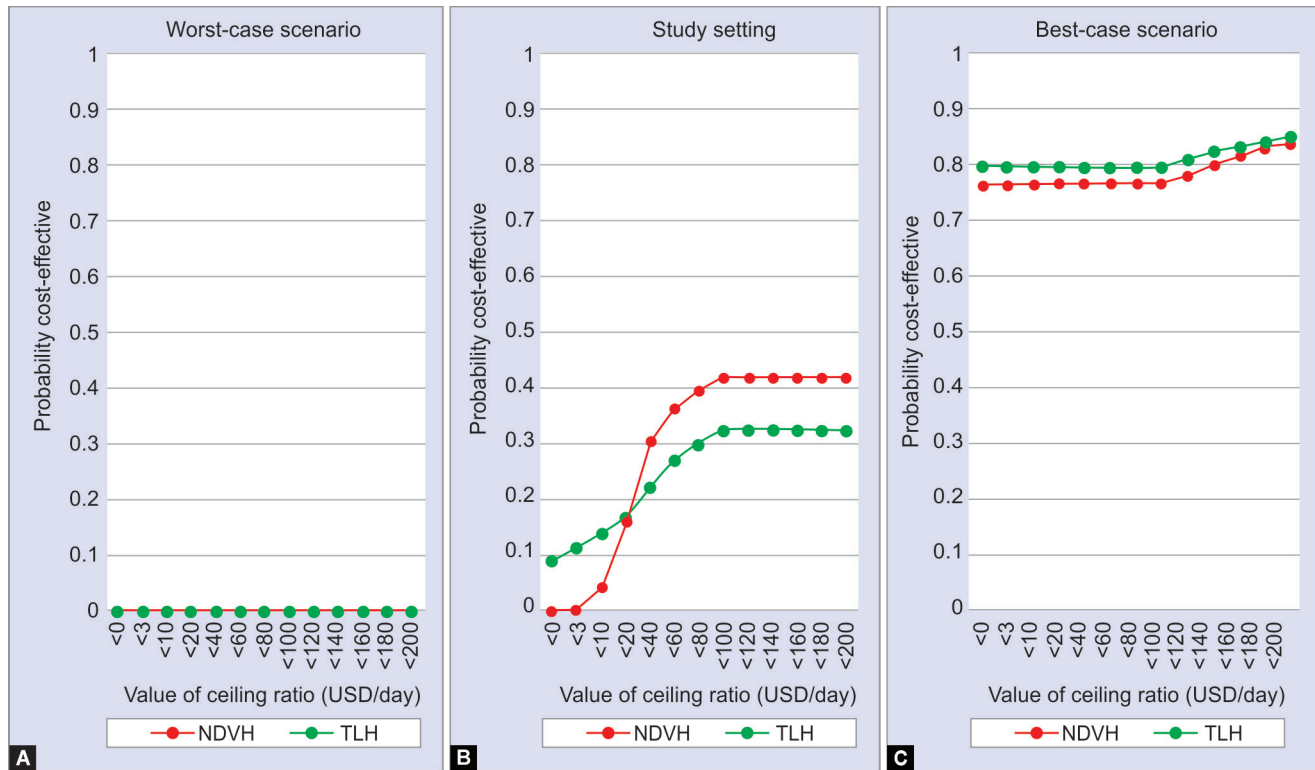
Fig. 1: Cost-effectiveness acceptability curves for study data, worst-case scenario, and best-case scenario

Table 3: Economic evaluation comparing NDVH and TLH to TAH

	TAH	NDVH	TLH	Significance[#] (p)
Time to recover	40.43 (34.91–45.95)	41.73 (33.31–50.16)	41.06 (31.06–51.07)	0.98*
Direct cost (mean, 95% CI)	659 (632–687)	800 (622–1116)	752 (719–795)	0.03*
Incremental effect (mean, 95% CI)		−1.09 (−11.82 to 8.04)	−0.58 (−13.16 to 9.02)	0.03
Incremental cost (mean, 95% CI)		143 (−49 to 470)	94 (49 to 142)	0.03
ICER (mean, 95% CI)		TAH dominant (TAH dominant to 477)	11 (TAH dominant to 351)	
Worst case				
Incremental effect (mean, 95% CI)		−11.84 (−20.94 to −4.92)	−11.05 (−22.46 to −3.12)	0.47[#]
Incremental cost (mean, 95% CI)		637 (403–1096)	642 (599–702)	0.72[#]
ICER (mean, 95% CI)		TAH dominant (TAH dominant to TAH dominant)	TAH dominant (TAH dominant to TAH dominant)	
Best case				
Incremental effect (mean, 95% CI)		2.99 (−5.12 to 10.42)	3.90 (−6.69 to 12.16)	0.054[#]
Incremental cost (mean, 95% CI)		−355 (−469 to −148)	−349 (−371 to −320)	0.76[#]
ICER (mean, 95% CI)		NDVH dominant (TAH dominant to 874)	TLH dominant (TAH dominant to 686)	

[#]Student's *t*-test; *ANOVA

used in clinical studies, and economic evaluations have been limited due to the inaccuracies in calculating disability weights.[15,17] The time to recover although subjective incorporates patient beliefs, effort, and optimism into the clinical outcome measure and mimics the real-life scenario.

Exclusion of an uncomplicated case from cost analysis would overestimate the costs for the remaining cases. The vice versa would apply for complicated cases. Therefore, all cases were included in the analysis. In terms of estimating costs, there were limitations due to assumptions that had to be adopted to

overcome logistical and financial constraints in a resource-poor setting.[14]

Top-down micro-costing was used for investigations, equipment, and utilities. Although bottom-up micro-costing would have been ideal, it would have added only a little improvement in accuracy at the cost of considerable time, effort, and money. Therefore, top-down micro-costing was used. It is an accepted practice to sacrifice a little accuracy to overcome feasibility issues if it is unlikely to improve the result.[15,17] Utility costs, such as electricity and water costs, were calculated using respective monthly bills divided by the average midnight total of patients, to obtain the cost of a particular utility per patient per day [e.g., electricity cost].[14] The average rate of utilization of equipment was considered to calculate equipment costs as there was no available information to assess the time duration of all procedures.[14] Adjustment for inflation was also not necessary due to the short duration of the study.[15,17]

While the RCT provided the framework, limitations of using a clinical trial as the main basis for an economic evaluation are well known.[15,17] However, in the absence of similar studies from low-resource settings, this study would provide valuable evidence. In order to overcome these shortcomings, a sensitivity analysis was done to estimate the cost as accurately as possible for which assumptions needed to be made which mimicked actual conditions. Therefore, the economic cost was considered instead of the financial cost to account for opportunity costs using the principle of discounting. Furthermore, the shelf life of surgical instruments was likely to be closer to a 5-year shelf life rather than 10 years. In addition, complications would also significantly affect the recovery and cost for a particular procedure. It is because of these reasons that the best-case scenario is likely to be the most realistic estimate of cost-effectiveness for a specialist center, whereas the worst-case scenario is likely to be representative of patients with complications.

The pragmatic design of the trial improved the generalizability and external validity of the study results that can be extrapolated to similar settings.[10] This study also provides level 1 evidence for the three main routes of hysterectomy and establishes a reproducible method of accessing surgical outcomes in a resource-poor setting. Although there was only a small difference among TAH, NDVH, and TLH in terms of clinical outcomes, the economic evaluation that considered both costs and effects elicited important differences that were too subtle to be detected when only the clinical outcomes were considered.

Conclusion and Clinical Significance

These results illustrate the importance of a composite viewpoint that considers both costs and consequences simultaneously as a bi-dimensional analysis rather than a conventional analysis of only consequences (one-dimensional). The standard TAH is likely to be the cost-effective method for the generalist, while the alternate routes NDVH and TLH are likely to be cost-effective in specialized centers.

Compliance with Ethical Standards

The trial was registered in the Sri Lanka clinical trials registry (SLCTR/2016/020) on July 26, 2016 (available from: http://slctr.lk/trials/515). The ethical review committee of the Faculty of Medicine, University of Kelaniya granted ethical approval for the study (P/12/01/2016). All participants gave informed written consent prior to participation in the study.

Supporting Information

Supporting information 1: CONSORT pragmatic trials checklist
Supporting information 2: CHEERS checklist
Supporting information 3: Survival analysis
Supporting information 4: Cox regression for analysis of covariates

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